

REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

Applicants respectfully request acceptance of the enclosed paper and electronic version of the sequence listing. In view of this, the application complies with the requirements for computer readable disclosure of the biological sequences under 37 C.F.R. §1.821-1.825.

1. Status Of Claims And Formal Matters

The specification has been amended to add sequence identifiers. No new matter has been added.

Claims 1-4, 11, 16, 22-23, 26-29 are under consideration in this application. Claims 1 and 16 have been amended, claims 24 and 25 are canceled, and claims 26-29 have been added. No new matter has been added by this amendment.

Support for the recitation of a fiber gene modified by homologous recombination between a plasmid comprising an adenovirus with a mutated fiber gene linearized at a nucleotide restriction site in the mutated fiber gene and a plasmid comprising a cDNA encoding the modified fiber comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob is found on page 72 lines 12 to 21 and continuing on page 73 lines 1 to 13 and Figure 5, of the specification as originally filed.

Support for the specific insertion of a SmaI site as a restriction site present only within the fiber gene is found on page 52, lines 7 to 16 of the specification as originally filed.

Support for the recitation of a fiber gene modified by homologous recombination in a bacterium between a plasmid comprising an adenovirus with a mutated fiber gene linearized at a nucleotide restriction site in the mutated fiber gene and a plasmid comprising a cDNA encoding the modified fiber comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob is found on page 71 lines 19 to 21 and continuing on page 72 lines 1 to 11, Example 23 and Figure 5 of the specification as originally filed.

Claims 1 and 16 have been amended without prejudice, without admission, and without surrender of subject matter, and without any intention of creating any estoppel as to equivalents to recite the base claim and intervening claims.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

2. The Objections to the Specification Are Overcome

The disclosure was objected to because of sequence informalities. Applicants have amended the specification to recite sequence identifiers and submit a sequence listing on paper and in computer-readable form plus a statement to support filing and submission in response to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures, thereby rendering the objection moot.

It is believed that the objections have been overcome. Reconsideration and withdrawal are respectfully requested.

3. The Rejections Under 35 U.S.C. § 112, First Paragraph, Are Overcome

Claims 1-4, 9, 11, 16, 22 and 23 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner alleges that the recitation 'homologous recombination between a plasmid comprising the fiber gene having a *Swa*I site and a plasmid comprising a cDNA encoding a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob' is not supported by the specification as filed. This rejection is respectfully traversed. This rejection is moot in light of the amendments to the claims submitted herein.

The objected recitation in claims 1 and 16 has been clarified to recite 'homologous recombination between a plasmid comprising an adenovirus with a mutated fiber gene linearized at a nucleotide restriction site in the mutated fiber gene and a plasmid comprising a cDNA encoding the modified fiber comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob', thereby obviating the rejection. Since claims 2-4, 9 and 11 depend from claim 1, and claims 22 and 23 depend from claim 16, the rejection to claims 2-4, 9, 11 and claims 22 and 23 have also been obviated.

It is believed that the rejections under 35 U.S.C. § 112, first paragraph, have been overcome. Reconsideration and withdrawal are respectfully requested.

4. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Are Overcome

Claims 1-4, 9, 11, 16, and claims 22-25 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner alleges that claims 1 and 16 are incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. This rejection is respectfully traversed. This rejection is moot in light of the amendments to the claims submitted herein.

Claims 1 and 16 have been clarified to include the recitation 'homologous recombination between a plasmid comprising an adenovirus with a mutated fiber gene linearized at a nucleotide restriction site in the mutated fiber gene and a plasmid comprising a cDNA encoding the modified fiber comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob', thereby obviating the rejection. Since claims 2-4, 9, 11 depend from claim 1, and claims 22 and 23 depend from claim 16, the rejection to claims 2-4, 9, 11, 22 and 23 has also been obviated. Claims 24 and 25 have been canceled.

Claim 22 recites the limitation 'said tumor cell'. The Examiner alleges that there is an insufficient antecedent basis for this limitation in the claim and suggests replacing the limitation with 'tumor cells'. Accordingly, claim 22 has been clarified to include the recitation 'tumor cells'.

It is believed that the rejections under 35 U.S.C. § 112, second paragraph, have been overcome. Reconsideration and withdrawal are requested.

5. The Rejections Under 35 U.S.C. § 102(e) Are Overcome

Claims 1-4, 9 and 11 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Wickham *et al.* (U.S. Patent No. 5,846,782, hereinafter "Wickham"). The Examiner contends that Wickham anticipates the claimed invention because Wickham teaches modification in the HI loop, including insertion of RGD peptide, and gene transfer in tumor cells. This rejection is respectfully traversed. This rejection is moot in light of the amendments to the claims submitted herein. The cited reference does not anticipate the instant invention.

The instant invention relates to a recombinant adenovirus comprising a fiber gene that is modified by homologous recombination between a plasmid comprising an adenovirus with a mutated fiber gene linearized at a nucleotide restriction site in the mutated fiber gene and a plasmid comprising a cDNA encoding the modified fiber comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob.

It is respectfully pointed out that a two-prong inquiry must be satisfied in order for a Section 102 rejection to stand. First, the prior art reference must contain all of the elements of the claimed invention. *See Lewmar Marine Inc. v. Barient Inc.*, 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Second, the prior art must contain an enabling disclosure. *See Chester v. Miller*, 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). A reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. *See In re Donohue*, 226, U.S.P.Q. 619, 621 (Fed. Cir. 1985).

Applying the law to the instant facts, the reference relied upon by the Office Action does not disclose, suggest or enable Applicants' invention. Claim 1 has been clarified to recite 'a recombinant adenovirus comprising a fiber gene that is modified by homologous recombination between a plasmid comprising an adenovirus with a mutated fiber gene linearized at a nucleotide restriction site in the mutated fiber gene and a plasmid comprising a cDNA encoding the modified fiber comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob'.

Wickham does not teach or suggest generating a fiber gene modified by **homologous recombination** between a plasmid comprising an adenovirus with a mutated fiber gene linearized at a nucleotide restriction site in the mutated fiber gene and a plasmid comprising a cDNA encoding the modified fiber comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob. For example, Wickham relates to exchanging the knob region of the Ad5 with the knob region from Ad2 since the HI loop of Ad2 contains a unique SpeI restriction site for standard cloning of target sequences (see, e.g., col. 21, lines 30 to 37 and col. 31, lines 31 to 48 of Wickham). In another example, Wickham illustrates the recombination of an adenovirus digested with SalI and a plasmid containing E4 regions (see, e.g., col. 25, lines 21 to 38). In yet another example, Wickham relates to the construction of

vectors that modify the fiber protein at the C-terminus with overlapping synthetic oligonucleotides (see, e.g., Example 6, col. 27-col. 30, line 53 of Wickham).

Since Wickham does not teach or suggest generating a fiber gene that is modified by homologous recombination between a plasmid comprising an adenovirus with a mutated fiber gene linearized at a nucleotide restriction site in the mutated fiber gene and a plasmid comprising a cDNA encoding the modified fiber comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob, Wickham does not contain each and every element of the claimed invention. It is submitted that the rejection of claim 1 has been obviated. Since claims 2-4, 9 and 11 depend from claim 1, it is submitted that the rejections to claims 2-4, 9 and 11 have also been obviated. It is also submitted that new claim 26 and 27 patentable over Wickham as claims 26 and 27 relate to a plasmid containing the fiber gene linearized at the Swal nucleotide restriction site 5'ATTTAAAT3'. It is also submitted that new claims 28 and 29 are patentable over Wickham as claims 28 and 29 relate to fiber gene modified by homologous recombination in bacterium.

Consequently, reconsideration and withdrawal of the Section 102 rejections are earnestly requested.

6. The Rejections Under 35 U.S.C. §103 Are Overcome

Claims 16, 22 and 23 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wickham. The Examiner alleges that Wickham teaches modification in the HI loop and gene transfer in tumor cells, but does not teach a method of transducing primary tumor cells wherein the tumor cell is a cancer ascite sample of a primary tumor explant. The Examiner contends that Wickam provided motivation for *in vitro* transduction of primary tumor cells. This rejection is respectfully traversed. This rejection is moot in light of the amendments to the claims submitted herein. The cited reference does not make the instant invention obvious.

The Examiner is respectfully directed to the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious

unless the prior art suggests the desirability of the modification.” For the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

Claim 16 has been clarified to recite that a fiber gene modified by homologous recombination between a plasmid comprising an adenovirus with a mutated fiber gene linearized at a nucleotide restriction site in the mutated fiber gene and a plasmid comprising a cDNA encoding the modified fiber comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob. As stated above, there is no teaching, suggestion or motivation in Wickham to generate a recombinant fiber gene modified by homologous recombination between a plasmid comprising an adenovirus with a mutated fiber gene linearized at a nucleotide restriction site in the mutated fiber gene and a plasmid comprising a cDNA encoding the modified fiber comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob. It is submitted that the rejection of claim 16 has been obviated. Since claims 22 and 23 depend from claim 16, it is submitted that the rejections to claims 22 and 23 have also been obviated. It is also submitted that new claims 26 and 27 are patentable over Wickham as claims 26 and 27 relate to a plasmid containing the fiber gene linearized at the *Swa*I nucleotide restriction site 5'ATTTAAAT3'. It is also submitted that new claims 28 and 29 are patentable over Wickham as claims 28 and 29 relate to fiber gene modified by homologous recombination in bacterium.

Consequently, reconsideration and withdrawal of the Section 103 rejections are earnestly requested.

REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested and the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the remarks, amendments and sequence listing, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,
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